PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32343A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/02251	International filing date *(day/month/year)* 05.03.2003	Priority date *(day/month/year)* 06.03.2002
International Patent Classification (IPC) or both national classification and IPC C07D417/04		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.08.2003	22.03.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Boletti-Cremers, K Telephone No. +49 89 2399-8541

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/02251

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-16	as originally filed

Claims, Numbers

1, 2, 3 (part), 4-15	received on 13.10.2003 with letter of 09.10.2003
3 (part)	filed with telefax on 03.03.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 13-15

   because:

   ☒ the said international application, or the said claims Nos. 13-15 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations

   see separate sheet

POINT III.

For the assessment of the presently worded claims 13-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise as industrially applicable claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment or diagnosis (see following remark under point V, 1.1) and the use of such a compound for the manufacture of a new medical treatment.

POINT V .

The following documents , quoted in the I.S.R., have been considered as relevant for the examination of the present application . Their numbering will be adhered to for the rest of the procedure.

(1) US-A-3 014 041.
(2) WO-A-01 77720 & EP-A- 1273 933,(2003-01-08) **(hereinafter called (2a)-copy provided).**
(3) EP-A-0 527 433 .
(4) Collection of Czechoslovak Chemical Communications , vol. 66, 2001, pp. 855-69.

1. Novelty.

1.1 In view of present reformulation of claim 3 which now stipulates that the compounds of (1) which should be avoided also encompass their acid addition salts, the novelty of the claimed matter with respect to the content of (1) can be acknowledged .

A special comment should be added, which concerns present (unamended) claim 1. Since the compounds of (1) do not relate to the use of the compounds disclosed there for the purpose of diagnosis , the novelty of said claim has been acknowledged on the basis of the EPO practice which permits the claim of a (known) compound for a certain medical/diagnosis purpose , provided that said purpose is not disclosed in the prior art.

1.2 Although (2a) , which is the later published EP-equivalent application of (2) , is not prior art according to the Chap II PCT proceedings , its content replaces the content of (2) (for obvious language reasons , the IPEA not being familiar with Japanese), which **is** prior art according to the Chap II PCT proceedings for the purpose of both examination of novelty and inventive step.

In view of the content of (2a) , the novelty of the claims on file can be acknowledged , because the various radicals R^1 and R^2 associated to the specific compounds of formula (1) of (2a) do not fall within the scope of the definitions of those associated to the R_3 and R_4 definitions of the compounds (I) on file.

1.3 None of the documents (3) and (4) discloses the biomarkers of present application as claimed and , consequently , the claimed matter can be regarded as novel with respect to their contents.

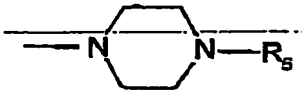
2. Inventive step

From all the documents quoted above , (4) represents the most relevant prior art because it relates to the same problem as the one of the application , namely to provide biomarkers, and relates (i.a.) to a compound, namely coumarin 6(3-(benzothiazo-2-yl)-7-(diethylamino)-2H-chromen-2 one), which is structurally very close to some of the compounds claimed for the same purpose.

In view of the fact that some of the biomarkers claimed are also very likely to be useful for the same purpose , the claimed 2- benzothiazolyle chromenes (Y: N , X : S) where R_3 and R_4 can be H, or CH_3 are not considered as inventive and the Applicant is invited to show either by argumentation or technical evidence , that those compounds on file possess any advantage or surprising feature when they are compared with the coumarin 6 of (4) in order to enable the acknowledgment of the inventiveness of the application with respect to the content of (4).

3. Formal Points.

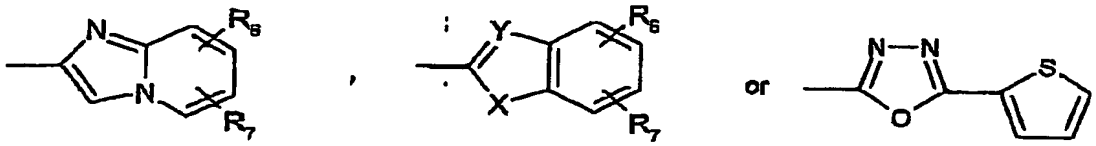
3.1 Documents (1)-(4) should be mentioned and briefly discussed in the description.



wherein R_5 is H, $(CH_2)_nI$, $(CH_2)_n{}^{123}I$, $(CH_2)_nOH$, CH_3, $^{11}CH_3$, $(CH_2)_nF$ or $(CH_2)_n{}^{18}F$, n being as defined above,

or one of R_1 and R_2 is hydrogen and the other, together with R_3, forms a $-(CH_2)_m-$ bridge, m being 2 or 3, and R_4 is H, CH_3, $(CH_2)_nI$, $(CH_2)_n{}^{123}I$, $(CH_2)_nOH$, $^{11}CH_3$, $(CH_2)_nF$ or $(CH_2)_n{}^{18}F$, and

R is a group of formula



wherein X is O, S or NR_9, R_9 being H, CH_3, $^{11}CH_3$, $(CH_2)_nI$, $(CH_2)_n{}^{123}I$, $(CH_2)_nOH$, $(CH_2)_nF$ or $(CH_2)_n{}^{18}F$ (n being as defined above), Y is CH or N and R_8 and R_7, independently, are H, NO_2, F, ^{18}F, $O(CH_2)_nF$, $O(CH_2)_n{}^{18}F$, Cl, CN, ^{11}CN, OCH_3, $O^{11}CH_3$, I, ^{123}I, $O(CH_2)_nI$ or $O(CH_2)_n{}^{123}I$ (n being as defined above),

in free base or acid addition salt form,

with the exception of

7-Dimethylamino-3-(1-methyl-1H-benzoimidazol-2-yl)-chromen-2-one
3-(1H-Benzoimidazol-2-yl)-7-dimethylamino-chromen-2-one
3-(6-Chloro-benzothiazol-2-yl)-7-dimethylamino-chromen-2-one
3-Benzothiazol-2-yl-7-dimethylamino-chromen-2-one
3-Benzooxazol-2-yl-7-dimethylamino-chromen-2-one
3-Benzooxazol-2-yl-7-methylamino-chromen-2-one
3-(5-Chloro-benzooxazol-2-yl)-7-dimethylamino-chromen-2-one
7-Amino-3-(1H-benzoimidazol-2-yl)-chromen-2-one
3-Benzothiazol-2-yl-7-dimethylamino-6-methyl-chromen-2-one
7-Dimethylamino-3-(1-ethyl-1H-benzoimidazol-2-yl)-chromen-2-one
7-Dimethylamino-3-(6-methoxy-benzothiazol-2-yl-chromen-2-one

in free base or acid addition salt form.